ESMO PRECEPTORSHIP ON
Small Cell Lung Cancer

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DISCLOSURES

Served on Advisory Boards: AstraZeneca; Pfizer; Boeringher

Honorarium to my institution: MSD, BMS, Roche, AstraZeneca, Pfizer, Boeringher

Travel Support: BMS, Roche, AstraZeneca
OUTLINE

- Extensive stage disease
- Limited stage disease
- Practice points in 2019
INTRODUCTION

- Accounts for 10-15% of newly diagnosed lung cancer
  - Incidence declining
- Majority (>95%) associated with tobacco smoking
- 1/3 present with limited stage only
- Rapid doubling times and early propensity to metastasise
- Initial sensitivity to chemotherapy with 60-80% RR
- Few patients will be long term survivors
  - High risk of local relapse
  - High risk of distant spread (brain)
- SCLC is characterised by multiple genetic abnormalities (RB-1, TP53, RASSF1, FHIT, MYC) but there are no approved targeted therapies
HOW DO WE STAGE SCLC?

Veterans Classification

- Limited vs. Extensive
- Based on encompassable radiation field

TNM Classification

![Graph showing survival rates for different stages of SCLC. The x-axis represents survival in years, and the y-axis represents the percentage of patients. The graph includes survival rates for different stages designated by Roman numerals (IA, IB, II, III, IV) with corresponding numbers indicating the number of patients. The legend notes that limited stage is T1-4 N0-3 M0.](image-url)
TREATMENT ALGORITHM IN SCLC IN 2019

**Limited Stage**
- Chemoradiation
  - Concurrent Cisplatin + etoposide with BD RT (45G; 30#)
  - PCI in (near) CR

**Extensive Stage**
- Platinum/etoposide x4-6
  - ?Thoracic RT if residual thoracic disease
    + PCI if no gross progression
- Platinum/etoposide x4-6
  - ?Thoracic RT if residual thoracic disease
    + MRI brain monitoring

**2nd Line options**
- Topotecan
- CAV
- Platinum/etoposide rechallenge (sensitive)

**3rd line:** nivolumab/pembrolizumab (if no previous immunotherapy)

**Platinum/etoposide + PD-L1 antibody:**
- Followed by maintenance PD-L1 antibody ± PCI

**PD-L1 antibody:** atezolizumab or durvalumab
TREATMENT ALGORITHM IN LS-SCLC IN 2019

SCLC

Limited Stage

Chemoradiation

Concurrent Cisplatin + etoposide with BD RT (45G; 30#)

PCI in (near) CR

Chemoradiation better than chemotherapy alone: 14% reduction in risk of death; p=0.001. Pignon et al. NEJM 1992

Concurrent chemoradiation better than sequential chemoradiation: 5yr survival 24% vs 18%. Takada et al. JCO 2002

Intergroup 0096: OS better in 45G/19D/30# (BD RT) than 45G/33D/25# (daily RT) with 4C chemo, p=0.04. At cost of higher G3 oesophagitis. Turrisi et al. NEJM 1999

CONVERT: Median OS similar between 45G/30# (BD RT) and 66G/33# (daily RT): 30m vs 25m, p=0.14. Toxicity similar with modern techniques. Faivre-Finn et al. Lancet Oncol 2017.

3 yr OS improved from 15.3% to 20.7% with PCI. Auperin et al. NEJM 1999
TREATMENT ALGORITHM IN ES-SCLC IN 2019

SCLC → Extensive Stage

Platinum/etoposide x4-6

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Platinum/etoposide/PD-L1 antibody
Followed by maintenance PD-L1 antibody ± PCI

2nd Line options
- Topotecan
- CAV
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3rd line: nivolumab/pembrolizumab (if no previous immunotherapy)

PD-L1 antibody: atezolizumab or durvalumab
**HISTORY OF CHEMOTHERAPY IN SCLC**

- Cyclophosphamide combination (CAV, CAE, CDE, CEV) – 80s
- Etoposide/Cisplatin (EP) = CAV, less toxic – 90s
- Metaanalysis (36 studies)
  - EP better than other combinations
- Metaanalysis (19 studies, 4054 pts)
  - Cisplatin 4.4% survival benefit at 1 year

**EP Efficacy:**
- ORR 70%
- PFS 5.5 m
- OS <10 m

**Accepted EP regimen:**
- Cisplatin 80mg/m² IV D1 + etoposide 100mg/m² IV D1,2,3 Q3 weekly x 4-6 cycles
- Cisplatin 60mg/m² IV D1 + etoposide 120mg/m² IV Q1,2,3 Q3 weekly x 4-6 cycles

**CISPLATIN OR CARBOPLATIN-BASED?**

Carboplatin- or Cisplatin-Based Chemotherapy in First-Line Treatment of Small-Cell Lung Cancer: The COCIS Meta-Analysis of Individual Patient Data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cisplatin-Based (n = 328)</th>
<th>Carboplatin-Based (n = 335)</th>
<th>All Patients (N = 663)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial</td>
<td>110 33.5</td>
<td>110 32.8</td>
<td>220 33.2</td>
</tr>
<tr>
<td></td>
<td>120 36.6</td>
<td>121 36.1</td>
<td>241 36.3</td>
</tr>
<tr>
<td></td>
<td>71 21.6</td>
<td>72 21.5</td>
<td>143 21.6</td>
</tr>
<tr>
<td></td>
<td>27  8.2</td>
<td>32  9.6</td>
<td>59  8.9</td>
</tr>
<tr>
<td>Age, years</td>
<td>67  66</td>
<td>67  67</td>
<td>67  67</td>
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<tr>
<td>Median Range</td>
<td>27-85</td>
<td>36-86</td>
<td>27-86</td>
</tr>
<tr>
<td></td>
<td>192 58.5</td>
<td>194 57.9</td>
<td>386 58.2</td>
</tr>
<tr>
<td></td>
<td>136 41.5</td>
<td>141 42.1</td>
<td>277 41.8</td>
</tr>
<tr>
<td>Sex</td>
<td>255 77.7</td>
<td>261 77.9</td>
<td>516 77.8</td>
</tr>
<tr>
<td></td>
<td>73  22.3</td>
<td>74  22.1</td>
<td>147 22.2</td>
</tr>
<tr>
<td>Stage</td>
<td>107 32.6</td>
<td>103 30.7</td>
<td>210 31.7</td>
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<tr>
<td>Limited disease</td>
<td>221 67.4</td>
<td>232 69.3</td>
<td>453 68.3</td>
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<tr>
<td>Extended disease</td>
<td>42 12.5</td>
<td>42 12.5</td>
<td>79 11.9</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>204 62.2</td>
<td>193 57.6</td>
<td>397 59.9</td>
</tr>
<tr>
<td>0</td>
<td>66 20.1</td>
<td>77 23.0</td>
<td>143 21.6</td>
</tr>
<tr>
<td>1</td>
<td>21  6.4</td>
<td>23  6.9</td>
<td>44  6.6</td>
</tr>
</tbody>
</table>

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Accepted Regimen:
Carboplatin AUC5 IV D1 + Etoposide 100mg/m² IV D1,2,3 Q3W x 4-6 cycles

Socinski et al. JCO 2009

Rossi et al. JCO 2012
TREATMENT ALGORITHM IN ES-SCLC IN 2019

SCLC → Extensive Stage → Platinum/etoposide x4-6
THORACIC IRRADIATION IN ES-SCLC?

CREST

ES SCLC without brain metastases or pleural involvement and response to 4-6 x Chemotherapy
N=483

1. EP: OS

PCI + TRT (30 Gy)

PCI only


Overall survival at:
1 year: 33% vs. 28% (p=0.066)
18 months: 16% vs. 9% (p=0.03)
2 years: 13% vs. 3% (p=0.004)

Slotman et al. Lancet 2014
POST HOC ANALYSIS OF CREST

With residual intrathoracic disease
Overall result 202/215 212/219 0.70 (0.57 – 0.85)
P<0.001

Without residual intrathoracic disease
Overall result 29/32 27/29 1.00 (0.59 – 1.70)
N.S.

Slotman et al. World Lung 2015
TREATMENT ALGORITHM IN ES-SCLC IN 2019

SCLC

Extensive Stage

Platinum/etoposide x4-6

?Thoracic RT if residual thoracic disease
PROPHYLACTIC CRANIAL IRRADIATION (PCI) IN ES-SCLC

Chemotherapy (4-6 cycles)

PCI reduces Risk of BMet, HR 0.27 p<0.0001 (Prim. EP)
Risk reduction of symptom. BMet after 1 Y: 15% vs. 40%

Med OS: 6.7 vs. 5.4
1 J: 27.1% vs. 13.3%
HR: 0.68 (0.52-0.88) p=0.003

CAVE: Negative effect on QL (alopecia, fatigue)

Slotman et al. NEJM 2007
ROLE OF PCI WITH MRI MONITORING

Key patient inclusion criteria:
- Extensive-disease SCLC
- Any response to first-line platinum doublet CT
- No BM by MRI assessment
- ECOG PS 0–2
  (n=163)

Arm A:
- Prophylactic cranial irradiation
  (n=84)
- Stratification
  - Age, ECOG PS, response, institution

Arm B:
- Observation alone
  (n=79)

• cMRI before start, then every 3 months

Primary endpoint
• OS

Takahashi T et al. Lancet Oncol 2017
ROLE OF PCI WITH MRI MONITORING

Takahashi T et al. Lancet Oncol 2017
TREATMENT ALGORITHM IN ES-SCLC IN 2019

SCLC

- Extensive Stage
  - Platinum/etoposide x4-6
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TOPOTECAN IN 2\textsuperscript{ND} LINE

- Topotecan 1.5g/m\textsuperscript{2} IV D1-5 Q3W vs. CAV (cyclophosphamide 1000mg/m\textsuperscript{2}, doxorubicin 45mg/m\textsuperscript{2}, vincristine 2mg D1 Q3W) for the treatment of recurrent SCLC (n=211)
- Progressive SCLC at least 60 days after completion of 1\textsuperscript{st} line chemotherapy (78% had received platinum/etoposide)

\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{Response to Treatment} & \textbf{Topotecan (n=107)} & \textbf{CAV (n=104)} & \textbf{P} \\
\hline
\textbf{Responders} & & & \textbf{.300} \\
Complete response & 0 & 0.0 & 1 & 1.0 \\
Partial response & 26 & 24.3 & 18 & 17.3 \\
Total & 26 & 24.3 & 19 & 18.3 \\
\textbf{95\% CI} & 16.2-32.4 & 10.8-25.7 & & \\
\hline
\textbf{Nonresponders} & & & \textbf{.552} \\
Stable disease & 21 & 19.6 & 12 & 11.5 \\
Progressive disease & 49 & 45.8 & 55 & 52.9 \\
Not assessable & 11 & 10.3 & 18 & 17.3 \\
Total & 81 & 75.7 & 85 & 81.7 \\
\hline
\textbf{Total patients} & 107 & 100.0 & 104 & 100.0 \\
\hline
\end{tabular}

\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Time-to-Event Parameters, weeks} & \textbf{Topotecan} & \textbf{CAV} & \textbf{P} \\
\hline
Response duration & n = 26 & n = 19 & \textbf{.300} \\
\textbf{Median} & 14.4 & 15.3 & \\
\textbf{Range} & 9.4-50.1 & 8.6-69.9* & \\
Time to response & n = 26 & n = 19 & \textbf{.953} \\
\textbf{Median} & 6.0 & 6.1 & \\
\textbf{Range} & 2.4-15.7 & 5.1-18.1 & \\
Time to progression & n = 107 & n = 104 & \textbf{.552} \\
\textbf{Median} & 13.3 & 12.3 & \\
\textbf{Range} & 0.4-55.1 & 0.1-75.3* & \\
Survival & n = 107 & n = 104 & \textbf{.795} \\
\textbf{Median} & 25.0 & 24.7 & \\
\textbf{Range} & 0.4-90.7* & 1.3-101.3 & \\
\hline
\end{tabular}

\*Estimate corresponds to a censored event.

Von Pawelek et al. JCO 1999
TREATMENT ALGORITHM IN ES-SCLC IN 2019

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2nd Line options

• Topotecan
• CAV
PLATINUM/ETOPOSIDE RECHALLENGE IN SENSITIVE RELAPSED SCLC: GFPC 13-01

Sensitive relapsed SCLC (> 90 days from D1 of the last cycle of chemotherapy)
ECOG PS 0-2, age > 18 years
Stratification:
PS
Institution
Response to first line

Carboplatin Etoposide
Carboplatin AUC 5 Day 1
Etoposide 100 mg/m2 on day 1-3 IV
Q 3wX6 courses
GCSF is recommended in primary prevention

Topotecan (oral)
2.3 mg/m2 on day 1-5 oral
Q 3wX6 courses

Primary endpoint: PFS
Secondary endpoints: OS, ORR (RECIST v1.1, central review), Safety, Quality of Life

Monnet et al. WCLC 2019
GFPC 13-01 RESULTS

Primary Endpoint: PFS

- Median PFS: 2.7 vs 4.7 mo (p<0.001)
- HR 0.6 (95% CI 0.4-0.8)

Secondary Endpoint: OS

- Median OS: 7.4 vs 7.5 mo (p=0.94)
- HR 0.99 (95% CI 0.7-1.3)

Neutropenia was higher in the topotecan arm than carbo/etop arm (p=0.035) and 2 treatment related deaths were observed in topotecan arm (due to febrile neutropenia)

Secondary Endpoint of ORR: 25% (topotecan) vs 49% (carbo/etop), p=0.002

Monnet et al. WCLC 2019
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2nd Line options

• Topotecan
• CAV
• Platinum/etoposide rechallenge (sensitive)
IMMUNOTHERAPY

- SCLC has low PD-L1 expression on tumour cells
- PD-L1 expression in SCLC is usually on immune/stromal cells
- Compared to NSCLC, SCLC has lower T cell density, T cell diversity, and T cell clonality despite similar TMB suggesting a more immunosuppressive microenvironment
## PD-1 ANTIBODIES AS 3\textsuperscript{RD} OR LATER LINE TREATMENT

<table>
<thead>
<tr>
<th>Study</th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>CheckMate 031\textsuperscript{1}</td>
<td>KN028+158\textsuperscript{2}</td>
</tr>
<tr>
<td>No of patients</td>
<td>109</td>
<td>83</td>
</tr>
<tr>
<td>ORR by BICR (%)</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Median time to response (mo)</td>
<td>1.6</td>
<td>2.1</td>
</tr>
<tr>
<td>Median duration of response (95% CI), mo</td>
<td>17.9 (7.9-42.0)</td>
<td>NR (4.1-35.8+)</td>
</tr>
<tr>
<td>Median PFS (95% CI), mo</td>
<td>1.4 (1.3-1.6)</td>
<td>2.0 (1.9-3.4)</td>
</tr>
<tr>
<td>Median OS (95% CI), mo</td>
<td>5.6 (3.1-6.8)</td>
<td>7.7 (5.2-10.1)</td>
</tr>
</tbody>
</table>

Both approved by FDA for this setting

1. Ready et al. JTO 2019; 2. Chung et al. AACR 2019
# PD1 AND PDL1 ANTIBODIES AS 2\textsuperscript{ND} LINE AND MAINTENANCE THERAPY

<table>
<thead>
<tr>
<th>Second line</th>
<th>IFCT-1603\textsuperscript{1} (n=73)</th>
<th>CheckMate 331\textsuperscript{2} (n=549)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>Chemotherapy n=24</td>
<td>Nivolumab N=284</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>2.3</td>
<td>10</td>
</tr>
<tr>
<td>DCR (%)</td>
<td>20.9</td>
<td>65</td>
</tr>
<tr>
<td>PFS</td>
<td>1.4 (1.2-1.5)</td>
<td>4.3 (1.5-5.9)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>2.26 (1.30-3.93); p=0.004</td>
<td>1.41 (1.18-1.69)</td>
</tr>
<tr>
<td>OS</td>
<td>9.5</td>
<td>8.7</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.84, 95% CI 0.45-1.58; p=0.60</td>
<td>0.86 (0.72-1.04); p=0.11</td>
</tr>
</tbody>
</table>

1ST LINE IMMUNOTHERAPY: IMPOWER133 AND CASPIAN

**IMpower133**
Horn et al. NEJM 2018

- Patients with (N = 403):
  - Measurable ES-SCLC (RECIST v1.1)
  - ECOG PS 0 or 1
  - No prior systemic treatment for ES-SCLC
  - Patients with treated asymptomatic brain metastases were eligible

**Stratification:**
- Sex (male vs. female)
- ECOG PS (0 vs. 1)
- Brain metastases (yes vs. no)

**Induction (4 x 21-day cycles):**
- Atezolizumab (1200 mg IV, Day 1) + carboplatin + etoposide
- Placebo + carboplatin + etoposide

**Maintenance:**
- Atezolizumab
- Treat until PD or loss of clinical benefit

**Co-primary end points:**
- Overall survival
- Investigator-assessed PFS

**Key secondary end points:**
- Objective response rate
- Duration of response
- Safety

Thoracic RT not allowed

**CASPIAN**
Paz-Ares et al. Lancet 2019

- Treatment-naïve ES-SCLC
- WHO PS 0 or 1
- Asymptomatic or treated and stable brain metastases permitted
- Life expectancy >12 weeks
- Measurable disease per RECIST v1.1

**Primary endpoint:**
- OS

**Secondary endpoints:**
- PFS
- ORR
- Safety & tolerability
- Health-related QoL

Thoracic RT not allowed
PFS

**IMpower133**

Horn et al. NEJM 2018

**CASPIAN**

Paz-Ares et al. Lancet 2019
IMpower133
Reck et al. ESMO 2019

CASPIAN
Paz-Ares et al. Lancet 2019
OS IN KEY SUBGROUPS

**IMpower133**
Horn et al. NEJM 2018

**CASPIAN**
Paz-Ares et al. Lancet 2019
**QOL**

**IMpower133**
Califano et al. ESMO 2018

**CASPIAN**
Paz-Ares et al. WCLC 2019
**Predictive Biomarkers**

**IMpower133**
Reck et al. ESMO 2019

**CASPIAN**
Paz-Ares et al. WCLC 2019
SUMMARY FOR IMMUNOTHERAPY IN SCLC

- No role for immunotherapy in 2\textsuperscript{nd} line or maintenance setting

- In 1\textsuperscript{st} line (concurrent chemo + PD-L1 antibody)
  - IMpower133 and CASPIAN similar design, similar population
  - Similar results (OS HR 0.76, 0.73)
  - Similar “shape” of OS and PFS curves with divergence after 6 months. ?delayed/durable “response” in a small % of patients
  - Neither PD-L1 expression or bTMB is predictive
  - Practice changing but cost may be prohibitive in developing countries

- In 3\textsuperscript{rd} line setting - ?role for pembrolizumab and nivolumab in those that have not had immunotherapy previously
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3rd line:
nivolumab/pembrolizumab (if no previous immunotherapy)

PD-L1 antibody: atezolizumab or durvalumab
THE FUTURE?

- KEYNOTE 604 awaited
- ?Add thoracic RT to ES-SCLC
- ?with PARPi + temozolamide or cediranib or AZD1775
- ?Alisertib: selective small molecular AAKi

“Extending” SCLC
  - ?large cell neuroendocrine carcinoma
  - ?transformed SCLC from EGFR+ NSCLC
  - Extra-pulmonary small cell
PRACTICE POINTS IN SCLC IN 2019

- LS-SCLC
  - Concurrent chemotherapy (cisplatin+etoposide x4-6) with radiotherapy (45G/30# BD) starting early (1st or 2nd cycle of chemotherapy)
  - If near CR post chemoRT, PCI increases OS

- ES-SCLC
  - Platinum/etoposide x4-6 cycles followed by sequential thoracic RT if residual thoracic disease + either PCI if no progression or MRI monitoring without PCI
  - Platinum + etoposide + atezolizumab or durvalumab followed by maintenance atezolizumab or durvalumab (± PCI) improves OS compared to platinum + etoposide
  - 2nd line options include topotecan, CAV or platinum/etoposide (if sensitive disease)
  - 3rd line nivolumab or pembrolizumab if no previous immunotherapy
  - No clear biomarkers for immunotherapy
THANK YOU